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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,529	08/04/1999	SUSAN MARY KINGSMAN	9192.9USWO	7151

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/254,529	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-34,36-38 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26-34, 36-38, 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 09/29/03 has been acknowledged.

Claims24, 26-34, 36-38 and 40-43 are pending.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 24, 26-34, 36-38, 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description requirement**. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 05/28/03.

Response to arguments

The applicant argues that HIV RRE analogous systems may be found in other retroviruses and one skill in the art at the time of filing would have recognized that other Rev/RRE system could perform the same function as HIV Rev/RRE system. The applicants concluded that they were in the possession of the claimed genus.

However, this is found NOT persuasive because the scope of invention as claimed encompasses: i) any retroviral polynucleotide response element (PRE), which are responsive to any nucleus to cytoplasm transport factor (see claim 24 34, 37), ii)

any polynucleotides response element that is responsive to a functional equivalent of HIV Rev. and iii) a functional equivalent of rev response element. At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity. Furthermore the specification only disclosed a HIV Rev response element, which is responsive to HIV Rev. Besides HIV Rev response element, which is responsive to HIV Rev protein the specification fails to disclose any other functional equivalent of Rev response element and functional equivalent of HIV Rev protein. In addition, it is unclear what is included or excluded in a retroviral particle that comprises all or a portion of any oncoretroviral genome. Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Applicant were referred to the Interim guidelines on ***Written Description*** published December 21, 1999 in the Federal Register, Vol. 64, No. 244, pp. 71427-71440. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only disclosed HIV Rev response element (RRE), which is responsive to HIV Rev protein but fails to disclose any and all functional and/or structural variants of HIV LTR U3 and R regions that are Tat inducible, HIV Rev response element and HIV Rev protein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case the variants (as claimed) has been defined only by

a statement of function that broadly encompasses tat inducible activity or responsive to Rev which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. Furthermore the variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of HIV LTR, RRE and Rev protein. The undefined variations as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. (see Ngo and Rudinger). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the invention as claimed.

Claims 24, 26-34, 36-38, 40-43 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity and comprises HIV RRE responsive to HIV Rev, does not reasonably provide enablement for a retroviral particle and/or a DNA construct which when in the form of a DNA provirus comprises any functional equivalent of HIV RRE, retroviral polynucleotide response element (PRE) and/or HIV Rev protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the office action mailed on 05/28/03.

Response to arguments

The applicant argues that undue experimentation is not required in the instant case. The quantity of experimentation required to substitute Rev/RRE equivalents of HIV Rev/RRE is low. The applicant further argues that one skill in the art would be able to use the instant specification and knowledge available in the art at the time of filing to make a retroviral particle comprising any known Rev/RRE system.

However, this is found NOT persuasive because invention as claimed requires an undue amount of experimentation, since the specification as filed only teaches making a HIV based retroviral particle. The scope of invention as claimed encompasses: **i)** any retroviral polynucleotide response element (PRE), which are responsive to any nucleus to cytoplasm transport factor (see claim 24 34, 37), **ii)** any polynucleotides response element that is responsive to a functional equivalent of HIV Rev and **iii)** a functional equivalent of rev response element.

At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprising a HIV Rev response element (a PRE or a retroviral response element), which is responsive to HIV Rev (a nucleus to cytoplasm transport factor). Besides HIV Rev response element, which is responsive to HIV Rev protein the specification fails to disclose any functional equivalent of Rev response element and functional equivalent of HIV Rev protein.

State Of Art And Predictability: The earlier office action clearly provided the evidence that the mechanism by which HIV Tat induces HIV LTR is complex. HIV-1 Tat protein binds to a stem-loop structure at the 5' end of viral mRNA and relieves this inhibition by inducing a remodeling of the nucleosome arrangement downstream of the transcription-initiation site. Tat performs this activity by recruiting to the viral long terminal repeat (LTR) the transcriptional co activator p300 and the closely related CREB-binding protein (CBP), having histone acetyltransferase (HAT) activity. Integrity of the basic domain of Tat is considered essential for this interaction (Marzio et al PNAS 95(23):13519-13524, 1998, see abstract). Even though a common mechanism of Tat transactivation through TAR is shared by HIV-1 and HIV-2 and SIV, the respective Tat gene products are not interchangeable in their effects (Brady et al PNAS, 91:365-369, 1994, see page 365, col.2). Furthermore, the Rev response element (RRE) is a 244-nt region in the env gene of HIV-1 that mediates transport of viral mRNA from the nucleus to the cytoplasm. Initially, the Rev protein binds with high affinity and specificity to a highly structured 30-residue region of the stem-loop IIB domain often termed the Rev binding element (RBE). See Huang et al PNAS USA. 97(10): 5107-5112, 2000, page 5107 col.1. In type D retroviruses, such as the simian retrovirus type 1 (SRV-1),

genomic RNA is exported by cellular factor(s) that interact with a conserved cis-acting RNA element, the constitutive transport element (CTE) which is distinct from the REV-RRE system (Saavdra et al. Curr Biol. 7(9):619-28, 1997 page 619, see Conclusion). Besides REV-RRE system the applicant fails to disclose any polynucleotides response element or retroviral response element that is responsive to a nucleus to cytoplasm transport factor. In addition, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo and Rudinger). Furthermore given the applicant's disclosure it is unclear how one skill in the art would identify and use a functional equivalent of HIV Rev that would bind to a functional equivalent of Rev response element. The invention as claimed encompasses structural and/or functional variations in both RRE and Rev components, wherein function of one is defined as function of other. In addition it is unclear how one skill in the art would use the retroviral particles and DNA construct (as claimed) to transduce any target cell, since the applicant fails to disclose the claimed structural variants required to make the DNA construct and/or retroviral particles. Therefore, considering the state of the art at the time of filing the applicant has not presented enablement commensurate in scope with the claims.

Quantity Of Experimentation Required: Considering the state of the art at the time of filing making any and all Tat inducible promoters, variants of RRE or Rev that have REV/RRE-like functional activity is not considered routine in the art and without sufficient guidance to a specific variants (as claimed) the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the

accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838 (**571-272-0769**). The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998 (**571-272-0781**). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER